

PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Docket No: Q75926

Ryuichi MORISHITA, et al.

Appln. No.: 10/615,262

Group Art Unit: 1633

Confirmation No.: 5695

Examiner: Robert M. KELLY

Filed: July 9, 2003

For: MEDICAMENT COMPRISING HGF GENE

DECLARATION UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Ryuichi MORISHITA, hereby declare and state:

THAT I am a citizen of Japan, and reside at c/o 1-41-4, Senriyama-nishi, Suita-shi, Osaka ,
565-0851, Japan;

THAT I am the first inventor of the above-identified patent application;

THAT I attach hereto an up to date copy of my curriculum vitae;

THAT I obtained the qualification of MD from Osaka University Medical School in
Japan in 1987, and the qualification of Ph.D. from Osaka University Medical School in Japan in
1991.

THAT I currently hold a position as a professor of Division of Clinical Gene Therapy,
Osaka University Medical School,

I further declare and state as follows:

I am familiar with the Office Action mailed June 13, 2007, in which the Examiner rejects Claims 7-11 on the ground of nonstatutory double patenting as claiming an invention that is not patentably distinct from the invention claimed in claims 1-3 of USP 6,936,594 (Morishita et al.).

The Examiner appears to assert that Morishita et al. teaches treating the cerebrum at the objective site, which includes the subarachnoid space, citing page 10, last paragraph. The Examiner seems to assert that if the brain were experiencing insufficiency of peripheral circulation, the subarachnoid space would be considered an area affected by the insufficiency, and thus would be the site of administration of the gene. Thus, the Examiner asserts that treating cerebrovascular disorders by administering the HGF gene to the subarachnoid space teaches or suggests treating insufficiency of peripheral circulation by administering the HGF gene to the affected area.

For the following reasons, I respectfully disagree with the Examiner.

Claims 1, 2, and 3 of Morishita et al. relate to "treatment of cardiovascular disorders," "treatment of reduced blood flow," and "promoting cerebral angiogenesis," respectively, by administering HGF gene to the subarachnoid space. However, "treatment of cardiovascular disorders," "treatment of reduced blood flow," and "promoting cerebral angiogenesis," do not teach or suggest treatment of insufficiency of peripheral circulation or peripheral angiostenosis, by injection of the HGF gene into the subarachnoid space.

More specifically, the claims of Morishita et al. relate to the treatment of blood disorders in the brain, namely, cerebrovascular disorders. In contrast, the presently claimed invention relates to the treatment of insufficiency of peripheral circulation or peripheral angiostenosis.

U.S. Application No.: 10/615,262

3

One of ordinary skill in the art of medicine knows that brain is classified as part of the central nervous system. However, the term "central" is the antonym of the term "peripheral." My opinion is supported by Steadman's Medical Dictionary, 28th edition, a copy of which is submitted herewith. Steadman's Medical Dictionary defines the "brain" as "That part of the central nervous system contained within the cranium" (page 250, right column). In contrast, Steadman's Medical Dictionary defines "peripheral" as "opposite of central (centralis)" (page 1463, right column).

Therefore, in my opinion, the cerebrovascular disorders of Morishita et al. have no relevance to the insufficiency of peripheral circulation or peripheral angiostenosis of the present claims, and, as a result, the claims of Morishita et al. do not teach or suggest the presently claimed invention.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 2007/ Dec 05


Ryuichi MORISHITA

CURRICULUM VITAE

Name: Morishita Ryuichi
 Degree: MD, PhD
 Birthday: 5/12/1962
 Birthplace: Japan
 Citizenship: Japanese

Carrier:

4/81-3/87	MD(3/87)	Osaka University Medical School, Osaka, Japan Medicine
4/87-3/91	PhD(3/91)	Osaka University Medical School, Osaka, Japan Medicine
4/91-8/91	Postdoctoral Fellow	Osaka University Medical School Department of Geriatric Medicine (T. Ogihara)
8/91-4/94	Postdoctoral Fellow	Stanford University School of Medicine, Division of Cardiovascular Medicine (Victor J. Dzau)
5/94-96/9	Senior Research Associate	Osaka University Medical School Department of Geriatric Medicine (T. Ogihara)
5/94-96/8	Visiting Instructor	Stanford University School of Medicine, Division of Cardiovascular Medicine (Victor J. Dzau)
4/95-96/9	Research Fellow of the Japan Society for the Promotion of Science	
10/96-10/98	Assistant Professor	Department of Geriatric Medicine (T. Ogihara) Osaka University Medical School
5/94-present	Chief	Section of Gene Therapy Department of Geriatric Medicine (T. Ogihara) Osaka University Medical School
10/98-03/2004	Associate Professor	Department of Geriatric Medicine (T. Ogihara) Osaka University Medical School
10/98-03/2004	Associate Professor	Division of Gene Therapy Science (Y. Kaneda) Osaka University Medical School
10/98-03/2004	Chief	Section of Cardiovascular Medicine Division of Gene Therapy Science (Y. Kaneda) Osaka University Medical School
01/2000-present	Visiting Professor	The University of Hong Kong
03/2003-present	Professor	Division of Clinical Gene Therapy Osaka University Medical School (Donated by Dai-ichi Pharmaceutical)

Honors:

- 1991 Award in Japan Research Foundation for Clinical Pharmacology
1991-1992 Award in Japan Heart Foundation
1992-1994 Postdoctoral Fellowship Grant in American Heart Association, California
1993 Award in American Federation Clinical Research
1993 Upjohn Young Investigator Award in Cardiology, Stanford University
1994 Young Investigator Award of the Dr. C & F. Demuth Medical Foundation at the 15th Scientific Meeting of the International Society of hypertension in Melbourne, Australia.
1994 Award in American Federation Clinical Research
1994 Award in Second Conference "Hypertension and Vascular Metabolisms"
1994 Young Investigator Award in Japan Vascular Disease Research Foundation
1996 Young Investigator Award (First winner) in Japanese Circulation Society
1996 Young Investigator Award in Japanese Atherosclerosis Society
1996 Harry Goldbratt Award in Council of High Blood Pressure, American Heart Association
1997 Young Investigator Award in 11th International Symposium on Atherosclerosis
1997 Young Investigator Award in 1st annual meeting of the Society of Cardiovascular & Endocrinology
1998 Young Investigator Award in 71th annual meeting of the Society of Endocrinology
1999 Young Investigator Award in the annual meeting of the Society of Pharmacology
1999 Award in Japanese of Japan Medical Society
2001 Takamine Jokichi Award in 5th annual meeting of the Society of Cardiovascular & Endocrinology
2001 Young Investigator Award in 2nd annual meeting of the Japanese Society of Hypertension
2002 Sato Award in 27th annual meeting of the Japanese Circulation Society
2003 Japan Innovator Award in 1st meeting (Nikkei BP)
2003 Award from Minister of Education in 1st meeting
2005 Invitrogen-Nature-Biotechnology Award

Editorial: Circulation Research (1998-), Circulation (1999-), Hypertension (2006-), Journal of Atherosclerosis and Thrombosis (Associate Editor; 1999-2004), Japanese Circulation Journal (2000-), Current Drug Targets (2000-), Current Gene Therapy (2000-), Heart (2000-), Journal of Hypertension (2000-2003), Expert Review of Cardiovascular Therapy (2002-), Cancer Therapy (2003-), Medicinal Chemistry Reviews (2003-), Gene Therapy & Molecular Biology (2004-), Current Hypertension Reviews (2004-), Current Cardiology Reviews (2004-), Geriatrics Gerontology International (2004-), Expert Opinion on Therapeutic Targets (2004-), Recent Patent Reviews On Cardiovascular Drug Discovery (2005-), Current Medicinal Chemistry (2006-), Recent Patents in Biotechnology (2006-), International Journal of Biomedical Science (2006-)

Professional Societies:

Board; Japanese Society of Vascular Biology Organization, Society for Intellectual Property

Fellow: Council of Circulation, American Heart Association, Council of Atherosclerosis, American Heart Association, Council of High Blood Pressure, American Heart Association, American College of Angiology, Japanese Society of Nephrology, Japanese Society of Pharmacology, Japanese Society of Atherosclerosis, Japanese Society of Endocrinology, Japanese Society of Cardiovascular & Endocrinology

Member, Council of Basic Science, American Heart Association, International Society of

Nephrology, American Society of Gene Therapy, North American Vascular Biology Organization, Japanese Society of Hypertension, Japanese Society of Circulation, Japanese Society of Gerontology, Japanese Society of Internal Medicine Japanese Society of Gene Therapy

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bradycardiac

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branch

- brad-y-car-di-ac** (brad'ē-kur'dē-ak). Relating to or characterized by bradycardia. *syn* bradycardic.
- bra-dy-car-dic** (brad'ē-kur'dik). *syn* bradycardiac.
- bra-dy-cl-ne-si-a** (brad'ē-si-nē'sē-ā). *syn* bradykinesia.
- bra-dy-crot-ic** (brad'ē-krot'ik). Relating to or characterized by a slow pulse. [brady- + *G. krotos*, a striking]
- bra-dy-di-as-to-le** (brad'ē-dī-as'tō-lē). Prolongation of the diastole of the heart.
- bra-dy-es-the-si-a** (brad'ē-es-thē'sē-ā). Slow sensory perception. [brady- + *G. aisthēsis*, sensation]
- bradygastria** (brad'ē-gas'trē-ā). Decreased rate of electrical pacemaker activity in the stomach, defined as less than 2 cycles/minute for at least 1 minute. Normal activity is defined as an electrical signal at a frequency of 2-4 cycles per minute using cutaneous electrogastrography. May be associated with nausea, gastroparesis, irritable bowel syndrome, and functional dyspepsia.
- bra-dy-glos-si-a** (brad'ē-glos'sē-ā). 1. Slow or difficult tongue movement. 2. *syn* bradyarthria. [brady- + *G. glossa*, tongue]
- bra-dy-ki-ne-si-a** (brad'ē-kin-ē'sē-ā). A decrease in spontaneity and movement. One of the features of extrapyramidal disorders, such as Parkinson disease. *syn* bradykinesia. [brady- + *G. kinēsis*, movement]
- bra-dy-ki-net-ic** (brad'ē-ki-net'ik). Characterized by or pertaining to slow movement.
- bra-dy-ki-nin** (brad'ē-ki'nin). The nonapeptide Arg-Pro-Gly-Phe-Ser-Pro-Phe-Arg, produced from the decapeptide kallidin (bradykinin) that is produced from α-globulin by kallikrein, normally present in blood in an inactive form and similar to trypsin in action; b. is one of several plasma kinins, is a potent vasodilator, and is one of the physiologic mediators of anaphylaxis released from cytotoxic antibody-coated mast cells following reaction with antigen (allergen) specific for the antibody. *syn* kallidin 9, kallidin I, kinin 9. [brady- + *G. kinēō*, to move]
- bra-dy-ki-nin-o-gen** (brad'ē-ki-nin'ō-jen). *syn* kallidin.
- bra-dy-ki-nin-po-ten-ti-a-tor B** (brad'ē-ki'nin pō-ten'shē-ā-tōr). GIP-Gly-Leu-Pro-Phe-Arg-Pro-Lys-Ile-Pro-Pro; the undecapeptide precursor of bradykinin and the angiotensins.
- bra-dy-la-li-a** (brad'ē-lā'lē-ā). *syn* bradyarthria. [brady- + *G. lalia*, speech]
- bra-dy-lex-i-a** (brad'ē-lex'sē-ā). Abnormal slowness in reading. [brady- + *G. lexō*, word]
- bra-dy-lo-gi-a** (brad'ē-lō'jē-ā). *syn* bradyarthria. [brady- + *G. logos*, word]
- bra-dy-pep-si-a** (brad'ē-pep'sē-ā). Slowness of digestion. [brady- + *G. pepsis*, digestion]
- bra-dy-pha-gi-a** (brad'ē-fā'jē-ā). Slowness in eating. [brady- + *G. phagō*, to eat]
- bra-dy-pha-si-a** (brad'ē-fā'sē-ā). A form of aphasia characterized by abnormal slowness of speech. *syn* bradyphenia. [brady- + *G. phasis*, speaking]
- bra-dy-phe-mi-a** (brad'ē-fē'mē-ā). *syn* bradyphasia. [brady- + *G. phēmē*, speech]
- bradyphrenia** (brā-dē'frē-nē-ā). Slowness in mental processing due to a decreased ability to shift quickly from one conceptual pattern to another; most often seen with Parkinson disease. [brady- + -phrenia]
- bra-dyp-ne-a** (brad-ip-nē-ā). In the diphthong pn, the p is silent only at the beginning of a word. Although bradyphne'a is the correct pronunciation, the alternative pronunciation bradyphne'a is widespread in the U.S. Abnormal slowness of respiration, specifically a low respiratory frequency. [brady- + *G. pneō*, breathing]
- bra-dy-psy-chi-a** (brad'ē-sī'kē-ā). Slowness of mental reactions. [brady- + *G. psychē*, soul]
- bra-dy-rhyth-mi-a** (brad'ē-rith'mē-ā). *syn* bradycardia.
- bra-dy-sper-ma-tism** (brad'ē-sper'mā-tizm). Absence of ejaculatory force, so that the semen trickles away slowly. [brady- + *G. sperma* (spermat-), seed, + *ism*]
- bra-dy-sphyg-mi-a** (brad'ē-sfig'mē-ā). Slowness of the pulse; can occur without bradycardia, as in ventricular bigeminy when every alternate beat may fail to produce a peripheral pulse. [brady- + *G. sphygmos*, pulse]
- bra-dy-stal-sis** (brad'ē-stahl'sis). Slow bowel motion. [*G. bradys*, slow, + (*peri*) *stalsis*, contracting around]
- bra-dy-tel-e-o-ki-ne-si-a** (brad'ē-tel'ē-ō-kin-ē'sē-ā). Sudden arrest of a movement just before its intended termination, then after a pause it is completed slowly or by jerks; a symptom of cerebellar disease. *syn* bradytelokinesia. [brady- + *G. teleos*, complete, + *kinēsis*, movement]
- bra-dy-tel-e-o-ki-ne-sis** (brad'ē-tel'ē-ō-kin-ē'sis). *syn* bradytelokinesia.
- bra-dy-u-ri-a** (brad'ē-yū'rē-ā). Slow micturition. [brady- + *G. ouron*, urine]
- bra-dy-zo-ite** (brad'ē-zō'it). A slowly multiplying encysted form of sporozoan parasite typical of chronic infection with *Toxoplasma gondii*. It has also been called a merozoite or zoite; the complex of b.'s within an enclosing membrane has also been called a pseudocyst, though it is now regarded as a true cyst. [brady- + *G. zōē*, life]
- braille** (brāl). A system of writing and printing by means of raised dots corresponding to letters, numbers, and punctuation to enable the blind to read by touch. [Louis Braille, French teacher of blind, 1809-1852]
- Brails-ford** (brāl'sfōrd). James Frederick, English radiologist, 1888-1961. *see* B.-Morquio disease.
- Brain** (brān). Walter Russell, English physician, 1895-1966. *see* B. reflex.
- brain** (brān) [TA]. That part of the central nervous system contained within the cranium. *see also* encephalon. Cf. cerebrum, cerebellum. *See* page 251, B13. [A.S. *braegen*]
- eloquent b.**, those parts of the b. that control speech, motor functions, and senses, localization of which is important in treating b. tumors.
- split b.**, a b. in which the corpus callosum and usually the anterior and posterior commissures have been sectioned, usually to treat certain refractory epilepsies.
- visceral b.**, *syn* limbic system.
- brain-case** (brān'kās). *syn* neurocranium.
- brain-stem, brain stem** (brān'stem) [TA]. Originally, the entire unpaired subdivision of the brain, composed of (in anterior sequence) the rhombencephalon, mesencephalon, and diencephalon as distinguished from the brain's only paired subdivision, the telencephalon. More recently, the term's connotation has undergone several arbitrary modifications: some use it to denote no more than rhombencephalon plus mesencephalon, distinguishing that complex from the prosencephalon (diencephalon plus telencephalon); others restrict it even further to refer exclusively to the rhombencephalon. From both developmental and architectural viewpoints, the original interpretation seems preferable. *syn* truncus encephali [TA].
- brain-wash-ing** (brān'wash'ing). Inducing a person to modify attitudes and behavior in certain directions through various forms of psychological pressure or torture.
- bran** (brān). A by-product of the milling of wheat, containing approximately 20% of indigestible cellulose; a bulk cathartic usually taken in the form of cereal or special bran products.
- branch** (branch) [TA]. An offshoot; in anatomy, one of the primary divisions of a nerve or blood vessel. A branch. *see* ramus artery, nerve, vein. *syn* ramus (1) [TA].
- accessory meningeal b.**, *syn* pterygomeningeal artery.
- accessory meningeal b. of middle meningeal artery**, *syn* accessory b. of middle meningeal artery.
- accessory b. of middle meningeal artery** [TA], a b. of either the middle meningeal or maxillary artery in the infratemporal fossa and passing superiorly through the foramen ovale to supply the trigeminal ganglion, dura mater, and inner table of the skull.

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through the periosteum to the bone. SYN periosteotomy.
[G. *tomē*, incision]

osteous (per'e-ost'ē-ūs), SYN periosteal.

osteum, pl. per-i-os-te-a (per'e-ost'ē-ūm, -ā) [TA].

fibrous membrane covering the entire surface of a bone

articular cartilage and the areas where it attaches to

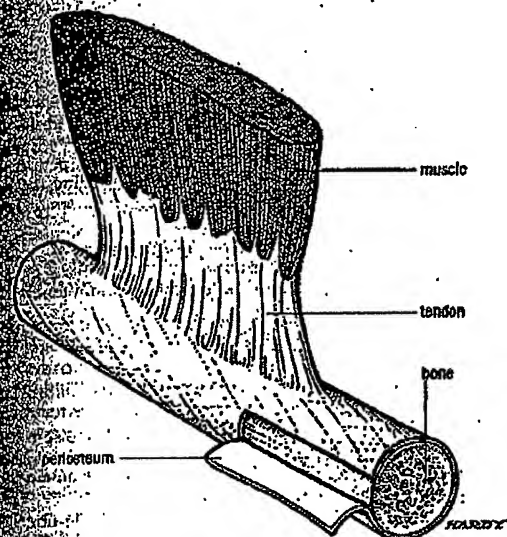
and ligaments. In young bones, it consists of two layers:

cellular layer that is osteogenic, forming new bone tissue.

outer fibrous connective tissue layer conveying the blood

and nerves supplying the bone; in older bones, the osteo-

layer is reduced. SEE ALSO perichondral bone. See this

perioste [Mod. L. fr. G. *periosteon*, ntr. of adj. *perioste-*around the bones, fr. *peri*, around, + *osteon*, bone]

olar, p. alveolare, SYN periodontium.

anli [TA], SYN pericranium.

os-ti-tis (per'e-ost'ē-tis), Inflammation of the periosteum.

osteitis.

os-to-ma (per'e-ost'ē-mā), SYN periosteoma.

os-to-sis, pl. per-i-os-to-ses (per'e-ost'ē-sis, -sēs).

osteosis.

os-tos-te-i-tis (per'e-ost'ē-tōs-tē-tis), Inflammation of a

with involvement of the periosteum. [periosteum + G. *ost-*bone, + *-itis*, inflammation]

os-to-tome (per'e-ost'ē-tōm), SYN periosteotome.

os-tot-o-my (per'e-ost'ē-tōt'ō-mē), SYN periosteotomy.

otic (per'e-ō'tik, -ō'tik), Surrounding the internal ear;

to the petrous portion of the temporal bone, or the spaces

and tissues in the bony labyrinth that surround the membranous

labyrinth. [peri- + G. *ous*, ear]

o-va-ri-tis (per'e-ō-vā-rē-tis), SYN perioophoritis.

o-vu-lar (per'e-ō-vyū-lār), Surrounding the ovum.

pach-y-men-in-gi-tis (per'i-pak'ē-men-in-jē-tis), In-

flammation of the area between the dura and bony covering of the

central nervous system. [peri- + pachymeninx (dura mater) + G.

inflammation]

pan-cre-a-ti-tis (per'i-pan'krē-ā-tē-tis), Inflammation

of the peritoneal coat of the pancreas.

pap-il-lar-y (per'i-pap'i-lār-ē), Surrounding a papilla.

per-i-pa-tet-ic (per'i-pā-tet'ik). 1. Walking around; formerly
used to describe a patient with "walking" (i.e., mild) typhoid
fever. 2. Relating to a disease imported to a nonendemic area by a
host clinically unaffected during the transport phase. [G. *peri-*
patēs, a walking about]

per-i-pe-ni-al (per'i-pē-nē-āl), Surrounding the penis.

per-i-pha-ryn-ge-al (per'i-fā-rin-jē-āl), Surrounding the
pharynx.per-iph-er-ad (pē-rif'ēr-ad), In a direction toward the periph-
ery. [G. *periphēria*, periphery, + L. *ad*, to]per-iph-er-al (pē-rif'ēr-āl) [TA]. 1. Relating to or situated at
the periphery. 2. Situated nearer the periphery of an organ or part
of the body in relation to a specific reference point; opposite of
central (centrals), SYN peripheralis [TA], eccentric (3).

per-iph-e-ra-lis (pē-rif'ēr-āl-is) [TA], SYN peripheral.

per-i-pher-in (per'if'er-in) [MIM*170710]. A glycoprotein ap-
parently necessary to maintain the shape of the outer segment disc
membranes of rods and cones; it is thought by many investigators
that a defect in p. is associated with certain types of blindness.per-iph-e-ro-cen-tral (pē-rif'ēr-ō-sen'trāl), Relating to both
the periphery and the center of the body or any part.per-iph-e-ry (pē-rif'ēr-ē), 1. The part of a body away from the
center; the outer part or surface. 2. SYN denture border. [G.
periphēria, fr. *peri*, around, + *pherō*, to carry]

per-i-phle-bit-ic (per'i-flē-bit'ik), Relating to periphlebitis.

per-i-phle-bi-tis (per'i-flē-bi'tis), Inflammation of the outer
coat of a vein or of the tissues surrounding it. [peri- + G. *phleps*,
vein, + *-itis*, inflammation]Per-i-pla-ne-ta (per'i-plā-nē'tā). A genus of large cockroaches
including several cosmopolitan household pests found wherever
food is available, especially in moist protected areas. *P. ameri-*
cana (American cockroach), a very large brownish-chestnut spe-

cies, 30-40 mm long, is probably native to Africa but now univer-

sally distributed; *P. fuliginosa* (the smoky-brown cockroach) is a

common household pest in the eastern and southeastern U.S.

[peri- + G. *planētēs*, a roamer]per-i-plasm (per'i-plazm), The space between the cell mem-
branes and the cell wall, in gram-negative bacteria; contains pro-
teins secreted by the cell.per-rip-lo-cin (pē-rip'lō-sin), A cardiotonic glycoside obtained
from the bark and stems of *Periploca grueca* (family As-clepiadaceae), a plant of southern Europe and Western Asia. [G.
periplokē, a winding around, fr. *plekō*, to twine, plait]per-i-po-lar (per'i-pō-lār), Surrounding the pole or poles of any
body, or any electric or magnetic poles.per-i-po-le-sis (per'i-pō-lē-sis), Penetration of migrating cells
between fixed tissue cells that are normally in close contact. [peri-
+ G. *pulomai*, to wander]

per-i-por-i-tis (per'i-pōr-i'tis), Miliary papules and papuloves-

icles with staphylococcal infection; most frequently on the face
and in infants. [peri- + G. *pore*, pore, + *-itis*, inflammation]per-i-por-tal (per'i-pōr'tāl), Surrounding the portal vein. SYN
peripylotic.per-i-proc-tic (per'i-prok'tik), SYN circumanal. [peri- + G.
prōktos, anus]per-i-proc-ti-tis (per'i-prok'ti'tis), Inflammation of the areolar
tissue about the rectum. SYN perirectitis.

per-i-pros-tat-ic (per'i-pros-tat'ik), Surrounding the prostate.

per-i-pros-ta-ti-tis (per'i-pros'tā-ti'tis), Obsolete term for in-

flammation of the tissues surrounding the prostate.

per-i-py-le-phle-bi-tis (per'i-pī-lē-flē-bi'tis), Inflammation
of the tissues around the portal vein. [peri- + G. *pylē*, gate, +*phleps*, vein, + *-itis*, inflammation]per-i-py-lic (per'i-pī'lik), SYN periportal. [peri- + G. *pylē*,
portal, gate]per-i-py-lor-ic (per'i-pī-lōr'ik, -pī-lōr'ik), Surrounding the py-
lorus.